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PLASMA ctDNA RAS STATUS SELECTS PATIENTS FOR ANTI-EGFR TREATMENT RECHALLENGE IN METASTATIC COLORECTAL CANCER: A META-ANALYSIS

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***Background*: Recently one randomized trial and several phase II studies underscored that patients with metastatic colorectal cancer who progressed after an initial clinical benefit from anti-epidermal growth factor receptor (EGFR) treatment may further benefit from rechallenge with anti-EGFR therapy. Testing circulating tumor DNA (ctDNA) RAS status prior to anti-EGFR rechallenge seems a promising non-invasive method to predict and monitor response to anti-EGFR readministration. *Aim*: To assess the capability of liquid biopsy ctDNA in exploring RAS status and in predicting outcome of metastatic colorectal cancer patients treated with anti-EGFR monoclonal antibody rechallenge. *Materials and Methods*: Systematic review of literature and meta-analysis of the available evidence. *Results*: Data from four studies involving 117 patients were available. All patients harbored RAS wild type tumors and derived benefit from first line anti-EGFR therapy. Of these, 65 underwent plasma ctDNA before anti-EGFR treatment rechallenge and were eligible for analyses: 35 patients had RAS wild type ctDNA, and 30 RAS mutated, indicating that 46% of patients underwent RAS status conversion after primary anti-EGFR therapy. Anti-EGFR rechallenge among patients with plasma ctDNA RAS wild type status was associated with a consistent benefit in progression free survival (hazard ratio (HR) 0.40, 95% confidence interval (CI) 0.22–0.70; $p = 0.001$; $I^2 = 0$) and overall survival (HR 0.37, 95% CI 0.16–0.85; $p = 0.02$; $I^2 = 74\%$) when compared to its use among patients with plasma ctDNA RAS mutation. Patients with plasma ctDNA RAS wild type profile also performed statistically better in term of disease control rate, risk for disease progression at 3 and 6 months, and risk for death at 6 and 12 months. *Conclusion*: RAS status assessment continues to be useful in predicting benefit for anti-EGFR treatment.**
***Key Words*: circulating tumor DNA, antiEGFR, panitumumab, cetuximab, NRAS, KRAS, BRAF.**

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The use of anti-epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab combined with cytotoxic chemotherapy has been shown to be effective in the treatment of wild-type KRAS colorectal cancer [1]. Little is, however, known about the possibility of anti-EGFR rechallenge in further lines of treatment. Recently, a small randomized trial and some phase II studies underscored that some patients with metastatic colorectal cancer, who progressed after an initial clinical benefit on anti-EGFR treatment, may further benefit from the use of anti-EGFR rechallenge [2].

Nonetheless, it has been shown that RAS mutation conversion may occur in up to 48% of patients over the course of treatment [3]. Therefore, the original assessment of RAS status might not be representative or useful for therapeutic decision making in further lines of treatment. Furthermore, even among patients remaining RAS wild type after initial anti-EGFR therapy, new driver mutations to other genes may be selected for leading to treatment resistance [4].

The question that arises is how we can screen patients who can benefit from anti-EGFR treatment rechallenge, specifically whether RAS status continues to be a valid marker for patient selection.

Liquid biopsy, by the detection of circulating tumor DNA (ctDNA) in plasma, due to its high specificity and sensitivity, is the most rapid and non-invasive modality by which we can easily explore and monitor tumor RAS status before, after and during the course of therapy. Testing ctDNA RAS status prior to anti-EGFR treatment rechallenge may constitute a promising non-invasive method to predict tumor response to anti-EGFR re-administration among pretreated patients [5, 6].

We therefore performed a systematic review of literature and meta-analysis in order to evaluate the cumulative available evidence for the use of ctDNA in exploring RAS status prior to treatment with anti-EGFR agents rechallenge among metastatic colorectal cancer patients. Our primary outcome was to validate the predictive utility of ctDNA RAS status in predicting response to anti-EGFR antibody re-administration.

The aim of the study is to assess the value of ctDNA liquid biopsy and RNA wildness in predicting response outcome to anti-EGFR re-administration (cetuximab or panitumumab) combined with chemotherapy among patient who progressed after having experienced clinical benefit to a previous treatment with anti-EGFR.

MATERIALS AND METHODS

Identification of studies. We searched PUBMED, SCOPUS, COCHRAN and ISI WEB OF KNOWLEDGE Central Register of Trials, without year and language restriction. We used (colon or rectal or colorectal) and (pantitumumab or cetuximab) and (rechallenge or retreat or repeat) as searching algorithm. The last search was updated in February 2020. Based on the title and abstract, we downloaded or requested full articles. Reference lists in these trials were checked to identify any other published or unpublished data.

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Abbreviations used: CI – confidence interval; ctDNA – circulating tumor DNA; EGFR – epidermal growth factor; GI – gastrointestinal; HR – hazard ratio; RR – relative risk.

In order to minimize the possibility to lose relevant data that couldn't be unearths by library searches, we hand-searched the references of review articles and evaluated symposia proceedings, poster presentations, and last five years major oncology conferences American Society of Clinical Oncology, European Society for Medical Oncology, American Society of Clinical Oncology GI, European Society for Medical Oncology GI. We also searched last five years of six major oncology journals (JCO, Lancet Oncology, Lancet, Annals of Oncology, New England, JAMA Oncology).

Primary outcome: summary survival analysis for the comprehensive available evidence for overall survival and progression free survival for anti EGFR re-challenged patient RAS ctDNA wild type *vs* RAS ctDNA mutant.

Secondary outcome: to assess eventual differences in the risk for death at 6 and 12 months, in the risk for progression at 3 and 6 months, in the disease control rate and disease progression among the two overmentioned populations.

Substrate for analyses were studies analyzing patient having received benefit from a previous anti-EGFR chemo-treatment regimen and who performed ctDNA analyses prior to proceed to a re-challenge with a further anti-EGFR chemo regimen and who proceed to treatment independently by the documented ctDNA RAS status.

Study eligibility. Patients included in the trial should have had RAS wild-type profile of patients in the initial tumor and progressed after having had a clinical benefit from a prior administration of an anti-EGFR chemo regimen treatment. All patients should have had a ctDNA liquid biopsy prior anti-EGFR treatment rechallenge with panitumumab or cetuximab for their metastatic colorectal cancer. Anti-EGFR treatment should have been rechallenged in combination with a chemo cytotoxic chemotherapy of documented activity in colorectal cancer. Combination with investigational agents of unconfirmed /investigational activity in colorectal cancer were excluded. If multiple publications were available for the same trial, we retrieved survival data from the most recent publication and the most informative. No year or language restriction was applied. Single arm studies evaluating treatment rechallenge only among ctDNA RAS wild type or only among ctDNA RAS mutant were excluded. Case report was also excluded.

Data extraction. From each eligible study we recorded authors' name, study's name, study's design, the number of patients initially scrutinized and the number of patients eligible and analyzed, the patients' performance status, the first treatment with anti-EGFR and the rechallenge regimen, the molecular profile, the response rate at the first line treatment and at the rechallenge, overall survival and progression free survival hazard ratios (HR) and their 95% CI, the number of deaths at 6 and 12 months, and the number of patients with progressive disease at 3 and 6 months.

Statistical analysis. For meta-analyses of the time-to-event outcomes (OS and PFS times), the most appropriate statistic is HR. If provided in a trial report, the HR and associated variances were used directly in the meta-analysis. HRs and 95% confidence intervals (CI) were pooled according to the inverse of variance method. An HR < 1 favored use chemotherapy among patients with RAS wild type ctDNA for any outcomes, except for Disease Control Rate (where a relative risk (RR) > 1 favored RAS wild type ctDNA patients group).

Risk ratio estimates were used at time point analyses for OS (6, 12 months) and PFS (3, 6 months). The methods described by Parmaret *et al.* [7] and Tierney *et al.* [8] were utilized to estimate HRs and RRs, when these data were not directly provided by the published studies. For this reason, the published Kaplan — Meier curves were used to reconstruct the sought data with the aid of a digitizing software in order to assure the highest precision possible [9]. The $\chi 2$ test of heterogeneity and the I2 statistic of inconsistency were used to assess heterogeneity among studies. Statistically significant heterogeneity was defined as a $\chi 2$ p-value < 0.1 or an I^2 statistic > 50%.

Since the number of studies analyzed were only 2–3 in each setting and considering that studies' sample sizes were very small but similar across trials, pooled estimates of HRs with their 95% CIs were calculated using the fixed-effects method, since random effect models might be not applicable in these circumstances [10].

Analyses were performed with RevMan 5.4.

RESULTS

Electronic searches yielded 418 hits: 83 from PubMed, 58 from Cochrane, 138 from Scopus and 139 from ISI Web of Knowledge. Of these, 372 were excluded by abstract or title and 45 by full text articles analyses. As a result, only one eligible trial was identified from databases searches [3]. Nonetheless, data from this trial available for analyses were presented only from a conference poster presentation [11]. Screening for abstracts of major oncology conferences led to the identification of three further eligible studies [12–14], even in these cases relevant data from these studies were available through their poster presentations [14, 15]. Overall data from four trials (E-RECHALLENGE, CRICKET, JACCRO CC-08 and JACCRO CC-09) involved 117 patients, 65 of them underwent plasma ctDNA testing before anti-EGFR rechallenge and were eligible for analyses: 35 patients with RAS wild type ctDNA, and 30 with RAS mutant ctDNA. All four trials were prospective. In all the studies, the ctDNA analysis performed prior anti-EGFR rechallenge was conducted optionally, did not drive the administration of treatment rechallenge and it was an exploratory endpoint. Two trials were presented as combined analyses JACCRO CC-08-09 [15]. Sample sizes were small and similar across trials (Table 1). All studies included patients with performance status less or equal than two and all trials were performed in 3rd or more line setting. In three studies treatment rechallenge was performed with cetuximab plus irinotecan (CRICKET, E-RECHALLENGE, JACCRO CC-08) while in JACCRO CC-09 panitumumab plus irinotecan was used. [11, 14, 15].

RAS conversion rate. All the patients included in the four trials were RAS wild type at baseline and have

had clinical benefit from first line anti-EGFR treatment + chemotherapy. Of note, ctDNA testing prior to anti-EGFR rechallenge revealed that 30/65 patients (46%) were RAS ctDNA mutant, underscoring that the proportion of patients undergoing RAS status conversion after treatment may be particularly high (Table 1) [11, 14, 15].

Primary outcomes. We found that anti-EGFR antibody rechallenge for patients with plasma ctDNA RAS wild type was associated with a consistent benefit in progression free survival when compared to its use among plasma ctDNA RAS mutant patients: in 65 analyzed patients from four studies, a HR 0.4 (95% CI 0.22–0.70) $p = 0.001$ was observed, with no study heterogeneity ($I^2 = 0$), (Fig. 1) [11, 14, 15]. Benefit favoring the plasma ctDNA RAS wild type population was also observed for overall survival. In three studies included (JACCRO 08-09, CRICKET) [11, 15], a cumulative HR 0.37 (95% CI 0.16–0.85) $p = 0.02$, was found, although the number of patients included was particularly low (41 patients), and large heterogeneity was observed $I^2 = 73.6$ (Fig. 2).

Secondary outcomes. No complete response was observed in either in ctDNA RAS wild type and in ctDNA RAS mutant population groups.

The proportion of progressing patients was notably higher among ctDNA RAS mutant patients (Risk of progression for ctDNA wild *vs* mutant status RR = 0.44, 95% CI 0.20–0.98) (Table 2). Accordingly, the proportion of patients at risk for disease progression at 3 months [RR = 0.44, 95% CI 0.23–0.83] and

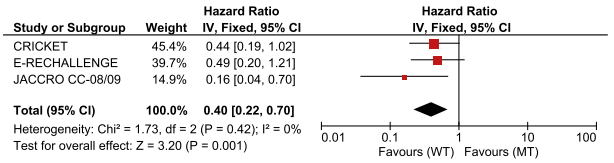

Fig. 1. Fixed effect model meta-analysis for progression free survival

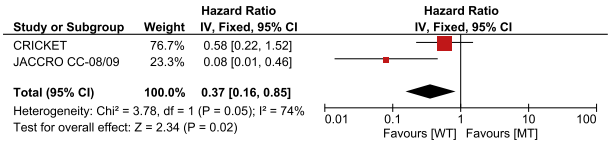

Fig. 2. Fixed effect model meta-analysis for overall survival

6 months [RR = 0.77, 95% CI 0.61–0.98] were statistically higher among ctDNA RAS mutant patients.

Conversely, disease control rate was statistically superior among ctDNA RAS wild type patients group [RR 1.74, 95% CI 1.11–2.73], and the risk of death both at 6 months [RR = 0.21, 95% CI 0.07–0.62] and 12 months [RR = 0.46, 95%CI 0.25–0.83] were statistically higher among ctDNA RAS mutant patients.

No study heterogeneity was observed for secondary outcomes (Table 2) (Appendix).

DISCUSSION

To the best of our knowledge, this is the first meta-analysis and full-paper peer-reviewed manuscript evaluating the role of ctDNA RAS assessment in predicting response to anti-EGFR antibody rechallenge

Table 1. Study characteristics and RAS conversion rate at anti-EGFR rechallenge

Study	All	Eligible	Original RAS status	1st line	Rechallenge	ctDNA Rechallenge baseline	Gene mutated (number of patients) *Molecular Analysis*	RAS conversion rate
JACCRO CC-08 JACCRO CC-09 (JACCRO CC-09/09AR)	58	16	RAS wild type	1st line cetuximab + Doublet JACCRO CC-08 (4pts) OR 1st line panitumumab + Doublet JACCRO CC-09 (12 pts) 2nd or 3rd line non anti-EGFR chemo	Irinotecan + Cetuximab (JACCRO CC-08) Irinotecan + Panitumumab (JACCRO-CC09)	RASwt 10 RASmut 6	KRAS Exon 2 codon 12 / Exon 3 codon 61 / NRAS exon 3 codon 61 (3), KRAS Exon 2 codon 12 / NRAS exon 3 codon 61 (1), KRAS Exon 2 codon 12 / Exon 3 codon 61 / NRAS exon 2 codon 12 (1), KRAS Exon 2 codon 12 / Exon 3 codon 61 (1) *OncoBEAMTMRAS CRC Kit.*	37%
CRICKET	28	25	RAS and BRAF wild type	1st line cetuximab + (FOLFIRI or FOLFOXIRI) 2nd line bevacizumab + (XELOX OR FOLFOXIRI or FOLFOX)	Irinotecan + Cetuximab	RASwt 13 RASmut 12	NRAS Q61L SD (1), KRAS G12V/ Q61H PD (1), KRAS G12V (4), KRAS G12D (6) *ddPCR for specific RAS and BRAF mutations, and ultra-deep next-generation sequencing (NGS) with Ion Torrent S5 XL (Thermo Fisher Scientific, Waltham, MA, USA).*	44%
E-RECHALLENGE TRIAL	33	24	RAS wild type	Earlier line cetuximab + Chemo Chemo line (after Cetuximab + Chemo) (all refractory to L-OHP, fluoropyrimidines, irinotecan, cetuximab and bevacizumab	Irinotecan + Cetuximab	RASwt 12 RASmut 12	KRAS A59 Q61 (2), KRAS G12 G13 (2), BRAF/KRAS G12 G13/ KRAS A59 Q61 (1), KRAS G12 G13/KRAS A59 Q61 (3), EGFR S492R /KRAS G12 G13/BRAF(1), BRAF /KRAS A59 Q61 (1), EGFR S492R (1), EGFR S492R /KRAS A59 Q61 (1) *ddPCR assays on a QX200 digital PCR system (BioRad laboratories) The PCR data were quantified as copies/µL using QuantaSoft™ software (BioRad laboratories).*	50%

Table 2. Fixed effects model meta-analyses for secondary outcomes: summary results (ctDNA RAS wild *vs* ctDNA RAS mutant)

	Studies N	Patients analyzed	Meta-analysis	RR	95% CI	*p*	I^2 statistics, %
Disease control rate [11, 14, 15]	4	64	Fix effects	1.74	(1.11–2.73)	0.02	0
Disease progression [11, 14]	2	49	Fix effects	0.44	(0.20–0.98)	0.04	0
3 months PFS [11, 14, 15]	4	65	Fix effects	0.44	(0.23–0.83)	0.01	0
6 months PFS [11, 14, 15]	4	65	Fix effects	0.77	(0.61–0.98)	0.03	0
6 months OS [11, 15]	3	41	Fix effects	0.21	(0.07–0.62)	0.005	0
12 months OS [11, 15]	3	41	Fix effects	0.46	(0.25–0.83)	0.01	0

in combination with cytotoxic chemotherapy. Patients with plasma ctDNA RAS wild type profile enjoyed superior disease control rate, PFS and OS compared to patients with ctDNA RAS mutation. Similarly, the risk of progression at 3 months and 6 months, and as well as the risk of death at 6 and 12 months was lower in ctDNA RAS wild type patients.

Overall, we can report that RAS status assessment continues to be useful in predicting benefit for anti-EGFR treatment even in the context of rechallenge when combined to irinotecan. Despite the probable presence of new driver-mutations induced by the selective pressure of antineoplastic therapy, host and microenvironmental milieu, these phenomena do not cancel the pivotal importance of RAS mutation status in defining biology and benefit from further anti-EGFR treatments.

The high proportion of patients with RAS status conversion after primary anti-EGFR treatment (almost 50% in our series) makes compulsory re-RAS profiling before rechallenge. However, tumor re-biopsy is invasive, may be associated with morbidity or be not feasible at all. Moreover, biopsy specimens may be not representative of the overall tumor biology due to intratumor heterogeneity. Indeed, the hypothesis of tumor heterogeneity and co-existence of both RAS mutated and RAS wild type clones in the primary tumor may partially explain the onset of resistance to anti-EGFR antibodies and subsequent treatment failure. Base on the Darwinian theory, the application of anti-EGFR leads to suppression of RAS wild type clones and further expansion of RAS mutated clones of the primary tumor ultimately responsible for anti-EGFR resistance. In addition, activating extracellular domain mutations may also explain the acquired resistance to anti-EGFR monoclonal antibodies administration [16, 17]. For these reasons, liquid biopsies constitute the most rapid and non-invasive modality by which we can easily explore and monitor the whole circulating tumor RAS status prior and during therapy. Due to its high specificity and improving sensitivity, the detection of ctDNA in the plasma may constitute the standard of care in this setting, upon further prospective validation.

The need of re-assessing RAS status after progression under an anti-EGFR chemo regimen is further underscored by the possible decay of RAS mutated clones after anti-EGFR therapy withdrawal. Thus, the use of high sensitivity circulating DNA can promptly identify patients who carry RAS wild type tumors and are candidates for anti-EGFR rechallenge therapy [17, 18].

Nonetheless, it should be underscored that, despite the statistical significance was evident for any setting and time-points analyzed, the results of this meta-analysis were based on only 65 patients recruited across four different trials (JACCRO CC-08, JACCRO CCC-09, E-RECHALLENGE and CRICKET). Thus, more extended data are needed to drive firm conclusions. Furthermore, since only four small studies were available and since sample sizes were particularly low, accurate analyzes by both fixed and random effect sizes were not feasible [10]. It should be also noted that a meta-analysis is based on published data and a meta-analysis of individual level data might define more clearly treatment benefits [19]. Trials included in our analyses identified data only from poster session of international conferences and not from peer-reviewed reports.

Allowing for these caveats, our study presents some novelties of paramount importance for clinical practice. Firstly, this is the first meta-analysis and the first full-paper peer-reviewed report evidencing that currently available ctDNA data support the value of ctDNA RAS status testing prior any treatment rechallenge with anti-EGFR agents in colorectal cancer. Secondly, considering that the proportion of patients with RAS status conversion after primary anti-EGFR treatment may be as high 50%, re-RAS profiling before rechallenge will improve clinical outcomes in patients with RAS wild type clones, and will prevent worthless costs avoiding the use of expensive targeted-treatments in patients harboring RAS mutations. Finally, the use of ctDNA could be advised as the novel standard biopsy modality in this setting since it is the most rapid and non-invasive method, and it overcomes tissue tumor re-biopsy limitations (feasibility, invasivity, potential morbidity, lack in representing overall tumor biology and intratumor heterogeneity).

Appendix: Appendix is available under request at smarovlahou@hotmail.com.

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ВІДБІР ХВОРИХ НА МЕТАСТАТИЧНИЙ КОЛОРЕКТАЛЬНИЙ РАК ДЛЯ ПОВТОРНОГО ЛІКУВАННЯ АНТИТІЛАМИ ПРОТИ EGFR, ВИХОДЯЧИ ІЗ ВИЗНАЧЕННЯ СТАТУСУ RAS У ЦИРКУЛЮЮЧІЙ ПУХЛИННІЙ ДНК У ПЛАЗМІ КРОВІ ХВОРИХ: МЕТААНАЛІЗ

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Стан питання: У нещодавно проведеному рандомізованому дослідженні та кількох клінічних дослідженнях II фази було показано, що у хворих на метастатичний колоректальний рак з прогресуванням процесу після позитивної відповіді на лікування антитілами проти рецептора епідермального фактора росту (EGFR) можна досягти подальшого позитивного клінічного результату після повторного застосування таких антитіл. Визначення статусу RAS у циркулюючій пухлинній ДНК (цпДНК) перед повторним застосуванням антитіл проти EGFR може стати обнадійливим неінвазивним методом для передбачення позитивної відповіді на таку повторну терапію та подальшого відстеження клінічної відповіді. ***Мета***: Оцінити спроможність рідинної біопсії цпДНК у визначенні статусу RAS та передбаченні результату лікування хворих на метастатичний колоректальний рак при повторному застосуванні моноклональних антитіл проти EGFR. ***Матеріали та методи***: Систематичний огляд літератури та метааналіз доступних результатів. ***Результати***: Доступними для аналізу виявилися дані чотирьох досліджень, які охоплювали 117 хворих. У всіх пацієнтів у пухлинних клітинах було визначено RAS дикого типу. Після застосування антитіл проти EGFR як терапії першої лінії у всіх цих хворих було досягнуто позитивного результату. У 65 пацієнтів перед повторним застосуванням антитіл проти EGFR було проаналізовано статус RAS у цпДНК. Дані щодо цих хворих були придатними для подальшого аналізу. Виявилося, що у 35 пацієнтів цпДНК містила RAS дикого типу, а у 30 хворих RAS був мутованим, тобто у 46% пацієнтів після першого курсу терапії відбулася конверсія статусу RAS. Повторний курс терапії антитілами проти EGFR у хворих з RAS дикого типу у цпДНК дав позитивний результат за показниками виживаності без прогресування (відношення ризиків (ВР) 0.40; 95% довірчий інтервал (ДІ) 0.22–0.70; p = 0.001; I^2=0) та загальної виживаності (ВР 0.37; 95% ДІ 0.16–0.85; p = 0.02; I^2 = 74%) у порівнянні з відповідними результатами в групі хворих, у яких було визначено мутацію RAS у цпДНК. У хворих з RAS дикого типу у цпДНК в плазмі крові кращими також були показники стабілізації процесу, ризику прогресування через 3 та 6 міс та ризику смерті через 6 та 12 міс. ***Висновки***: Визначення статусу RAS має предиктивне значення щодо результатів терапії антитілами проти EGFR.

Ключові слова: циркулююча пухлинна ДНК, антитіла проти EGFR, панітумумаб, цетуксимаб, NRAS, KRAS, BRAF.

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